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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,773	07/20/2006	Stephen Lloyd Michell	41577/321208	1870

23370 7590 11/06/2008

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
11/06/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,773	MICHELL ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-15 and 23-26* is/are pending in the application.

4a) Of the above claim(s) *8 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7,9-14 and 23-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/20/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 9/3/08 was entered.

Claims 2-15 and 23-26 are pending in the present application.

Applicant's election with traverse of the following species: (a) subspecies *tularensis* as a species of a strain of *Francisella tularensis*; and (b) purF as a species of a gene encoding an enzyme in the purine pathway, in the reply filed on 9/3/08 is acknowledged. The traversal is on the ground(s) that each species share a "special technical feature" in that each species acts as a protective vaccine against a similar genus of organism, and therefore it is not accurately to conclude that each species has different properties one from the others.

This is not found persuasive because: (a) Karlsson et al. (Microbial & Comparative Genomics 5:25-39, 2000; IDS) already teach explicitly that **on the basis of virulence, the growth requirement for cysteine, the presence or absence of capsule, citrulline ureidase activiety and the differential ability to produce acid from D-glucose, sucrose, and glycerol, four subspecies of *F. tularensis* have been prosposed** (page 26, second full paragraph). Thus, it is apparently clear that these subspecies do have different properties one from the others. (b) each of the genes coding for enzymes involved in the purine pathway is structurally and functionally differently one from the others, simply based on the different functions that they carry out (see Figure 2A in the Karlsson et al article).

The species requirement is still deemed proper and is therefore made FINAL.

Therefore, claims 8 and 15 are withdrawn from further consideration because they are directed to a non-elected species.

Accordingly, claims 2-7, 9-14 and 23-26 are examined on the merits herein with the above elected species.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2-7, 9-14 and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable Drabick et al. (Vaccine Research 6:67-74, 1997; IDS) in view of Karlsson et al. (Microbial & Comparative Genomics 5:25-39, 2000; IDS), Gray et al. (FEMS Microbiology Letters 215:53-56, 2002; IDS) and Gicquel et al. (US 6,261,568).

With respect to the elected species, Drabick et al already teach at least that active immunization of live vaccine strain (LVS) of *F. tularensis*, derived from *F. tularensis* biovar paleoartica (type B), provides protection against infection with a highly virulent FSC041 strain (*F. tularensis* biovar *tularensis* or type A) as well as the attenuated LVS strain in a mouse model, while immunization with highly attenuated rifampicin-resistant mutant of the LVS (Rif^r 7) and strain 38 only induced protection against challenge with the LVS in the same mouse model (see at least the abstract; page 70, section entitled "Active immunization study" and Table 3). Drabick et al attributed the failure of highly attenuated Rif^r 7 and strain 38 to induce effective cellular immunity to challenge with FSC041 to either a kinetic problem that is the immunizing organisms did not persist long enough to induce cellular immunity and immune T cells, or that these strains lack anigens critical for the development of cellular immunity (page 72, last two paragraphs).

Drabic et al do not specifically teach explicitly a pharmaceutical composition comprising a live strain of *Francisella* species (with *Franciscella tularensis* subspecies *tularensis* as the elected species) wherein a gene encoding an enzyme in the purine pathway has been inactivated (with purF as the elected species); and a method of preventing or treating infection by a *Francisella* species using the same.

However, at the effective filing date of the present application (3/27/03), Karlsson et al already disclosed assembled sequencing data for the *Francisella tularensis* Strain Schu 4 (***Franciscella tularensis* subspecies *tularensis***) genome, and genes encoding all of the enzymes in the purine biosynthetic pathway were identified (see at

least the abstract; Table 2; Fig. 2; Section entitled "Purine biosynthesis pathway proteins"). Karlsson et al further taught that **the data (including genes of the purine metabolic pathway as targets) can be used to develop defined rationally attenuated mutants of *F. tularensis*, which could be used as replacements for the existing genetically undefined live vaccine strains** (last sentence of the abstract; and title of the article). Karlsson et al further stated "Thus, our result to date suggest that the organism encodes only part of the known salvage pathway that has been described in *E. Coli*" (page 35, middle of third paragraph).

Additionally, Gray et al already constructed five attenuated transposon mutants of *Francisella novicida*, **one of which has an interrupted purF gene (CG 57 strain)**; and they found that all of the mutant strains **are compromised in their ability to grow in mouse macrophages *in vitro* but not in bacteriological media** (see at least the abstract; sections entitled "Recombinant DNA techniques, DNA sequencing and transposon mutagenesis" and "Isolation of transposon mutants"; page 55, col. 1, middle of first paragraph).

Furthermore, at the effective filing date of the present application Gicquel et al already taught the preparation of recombinant mycobacterium strains of pathogenic origin (e.g., *M. tuberculosis*, *M. leprae*) that have been attenuated by the inactivation of a gene coding for a protein necessary for the biosynthesis of a purine, including the purC gene or the purL gene (both of which are genes encoding enzymes that are active early in the purine pathway), wherein the recombinant strains have a reduced capacity to propagate in a mammalian host but remain viable in the host for a period of time

sufficient to induce a protective immune response against the natural pathogenic mycobacterium counterpart (see at least Summary of the Invention; example 2 and the claims).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the teachings of Drabick et al by also preparing an attenuated recombinant live strain of *Francisella tularensis subspecies tularensis* having at least an inactivated purF gene tin a pharmaceutical composition to induce protection against an infection by a *Francisella* species in an animal in light of the teachings of Karlsson et al., Gray et al and Gicquel et al. as discussed above.

An ordinary skilled artisan would have been motivated to carry out the above modification because Karlsson et al already taught that genes of the purine metabolic pathway in *Francisella tularensis strain Schu 4* can be used as defined targets for the construction of a rationally attenuated auxotrophic vaccine and to replace the existing genetically undefined live vaccine strains. Additionally, Gray et al already constructed successfully at least a transposon mutant of *Francisella novicida* containing an interrupted *purF* gene, that is found to be compromised in its ability to grow in mouse macrophages (an attenuated strain). Furthermore, Gicquel et al already taught that recombinant mycobacterium strains of pathogenic origin (e.g., *M. tuberculosis*, *M. leprae*) that have been attenuated by the inactivation of a gene coding for a protein necessary for the biosynthesis of a purine, are capable of inducing a protective immune response against the natural pathogenic mycobacterium counterpart.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Drabick et al., Karlsson et al., Gray et al. and Gicquel et al.; coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

At the effective filing date of the present application, Nikolich et al (US 6,444,445) already taught the preparation of live Brucella vaccines protective against brucellois, including the strain WRRP1 containing a purE deletion (purE is also a gene encoding an enzyme that is active early in the purine pathway).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN/

Primary Examiner, Art Unit 1633